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DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA1258]

Schedules of Controlled Substances: Placement of Zuranolone in Schedule IV

AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Interim final rule; request for comments.

SUMMARY: On August 4, 2023, the United States Food and Drug Administration approved a new drug application for ZURZUVAE (zuranolone) capsules for the treatment of post-partum depression. The Department of Health and Human Services provided the Drug Enforcement Administration (DEA) with a scheduling recommendation to place zuranolone and its salts in schedule IV of the Controlled Substances Act (CSA). In accordance with the CSA, as amended by the Improving Regulatory Transparency for New Medical Therapies Act, DEA is hereby issuing an interim final rule placing zuranolone, including its salts, in schedule IV of the CSA. This action facilitates the public availability of zuranolone as a schedule IV controlled substance.

DATES: This rule is effective [INSERT DATE OF PUBLICATION IN THE FEDERAL REGISTER]. Comments must be submitted electronically or postmarked on or before [INSERT DATE 30 DAYS AFTER PUBLICATION IN THE FEDERAL REGISTER].

Requests for hearing and waivers of an opportunity for a hearing or to participate in a hearing, together with a written statement of position on the matters of fact and law asserted in the hearing, must be received on or before [INSERT DATE 30 DAYS AFTER PUBLICATION IN THE FEDERAL REGISTER].

ADDRESSES: Interested persons may file written comments on this rulemaking in accordance with 21 U.S.C. 811(j)(3) and 21 CFR 1308.43(g). The electronic Federal Docket Management System will not accept comments after 11:59 p.m. Eastern Time on the last day of the comment period. To ensure proper handling of comments, please reference "Docket No. DEA1258" on all correspondence, including any attachments.

- *Electronic comments:* The Drug Enforcement Administration (DEA) encourages commenters to submit comments electronically through the Federal eRulemaking Portal, which provides the ability to type short comments directly into the comment field on the web page or attach a file for lengthier comments. Please go to *https://www.regulations.gov* and follow the online instructions at that site for submitting comments. Upon completion of your submission, you will receive a Comment Tracking Number for your comment. Submitted comments are not instantaneously available for public view on Regulations.gov. If you have received a Comment Tracking Number, your comment has been successfully submitted and there is no need to resubmit the same comment.

- *Paper comments:* Paper comments that duplicate electronic submissions are not necessary. Should you wish to mail a paper comment *in lieu of* an electronic comment, it should be sent via regular or express mail to: Drug Enforcement Administration, Attn: DEA Federal Register Representative/DPW, 8701 Morrissette Drive, Springfield, VA 22152.

- *Hearing requests:* All requests for hearing and waivers of participation, together with a written statement of position on the matters of fact and law asserted in the hearing, must be filed with the DEA Administrator, who will make the determination of whether a hearing will be needed to address such matters of fact and law in the rulemaking. Such requests must be sent to: Drug Enforcement Administration, Attn: Administrator, 8701 Morrissette Drive, Springfield, Virginia 22152. For informational

purposes, a courtesy copy of requests for hearing and waivers of participation should also be sent to: (1) Drug Enforcement Administration, Attn: Hearing Clerk/OALJ, 8701 Morrissette Drive, Springfield, Virginia 22152; and (2) Drug Enforcement Administration, Attn: DEA Federal Register Representative/DPW, 8701 Morrissette Drive, Springfield, Virginia 22152.

FOR FURTHER INFORMATION CONTACT: Terrence L. Boos, Drug & Chemical Evaluation Section, Diversion Control Division, Drug Enforcement Administration; Telephone: (571) 362-3249.

SUPPLEMENTARY INFORMATION:

Posting of Public Comments

Please note that all comments received in response to this docket are considered part of the public record. DEA will make comments available for public inspection online at *https://www.regulations.gov*. Such information includes personal or business identifying information (such as name, address, State or Federal identifiers, etc.) voluntarily submitted by the commenter. In general, all information voluntarily submitted by the commenter, unless clearly marked as Confidential Information in the method described below, will be publicly posted. Comments may be submitted anonymously. The Freedom of Information Act applies to all comments received.

Commenters submitting comments which include personal identifying information (PII), confidential, or proprietary business information that the commenter does not want made publicly available should submit two copies of the comment. One copy must be marked "CONTAINS CONFIDENTIAL INFORMATION" and should clearly identify all PII or business information the commenter does not want to be made publicly available, including any supplemental materials. DEA will review this copy, including the claimed PII and confidential business information, in its consideration of comments. The second copy should be marked "TO BE PUBLICLY POSTED" and must have all

claimed confidential PII and business information already redacted. DEA will post only the redacted comment on https://www.regulations.gov for public inspection.

For easy reference, an electronic copy of this document and supplemental information to this interim final rule (IFR) are available at *https://www.regulations.gov*.

Request for Hearing or Appearance; Waiver

Pursuant to 21 U.S.C. 811(a), this action is a formal rulemaking "on the record after opportunity for a hearing." Such proceedings are conducted pursuant to the provisions of the Administrative Procedure Act (APA), 5 U.S.C. 551–559.[1] Interested persons, as defined in 21 CFR 1300.01(b), may file requests for a hearing in conformity with the requirements of 21 CFR 1308.44(a) and 1316.47(a), and such requests must:

(1) state with particularity the interest of the person in the proceeding;

(2) state with particularity the objections or issues concerning which the person desires to be heard; and

(3) state briefly the position of the person with regarding to the objections or issues.

Any interested person may file a waiver of an opportunity for a hearing or to participate in a hearing in conformity with the requirements of 21 CFR 1308.44©, together with a written statement of position on the matters of fact and law involved in any hearing.[2]

All requests for hearings and waivers of participation, together with a written statement of position on the matters of fact and law involved in such hearing, must be sent to DEA using the address information provided above. The decision whether a hearing will be needed to address such matters of fact and law in the rulemaking will be made by the Administrator. If a hearing is needed, DEA will publish a notice of hearing

[1] 21 CFR 1308.41–1308.45; 21 CFR part 1316, subpart D.
[2] 21 CFR 1316.49.

on the proposed rulemaking in the *Federal Register*.[3] Further, once the Administrator determines a hearing is needed to address such matters of fact and law in rulemaking, she will then designate an Administrative Law Judge (ALJ) to preside over the hearing. The ALJ's functions shall commence upon designation, as provided in 21 CFR 1316.52.

In accordance with 21 U.S.C. 811 and 812, the purpose of a hearing would be to determine whether zuranolone meets the statutory criteria for placement in schedule IV.

Background and Legal Authority

Under the Controlled Substances Act (CSA), as amended in 2015 by the Improving Regulatory Transparency for New Medical Therapies Act (section 2(b) of Pub. L. 114-89), DEA is required to commence an expedited scheduling action with respect to certain new drugs approved by the Food and Drug Administration (FDA). As provided in 21 U.S.C. 811(j), this expedited scheduling is required where both of the following conditions apply: (1) The Secretary of the Department of Health and Human Services (HHS) has advised DEA that a New Drug Application (NDA) has been submitted for a drug that has a stimulant, depressant, or hallucinogenic effect on the central nervous system (CNS), and that it appears that such drug has an abuse potential; and (2) the Secretary of HHS recommends that DEA control the drug in schedule II, III, IV, or V pursuant to 21 U.S.C. 811(a) and (b). In these circumstances, DEA is required to issue an interim final rule (IFR) controlling the drug within 90 days.

Subsection 811(j)(2) states that the 90-day timeframe starts the later of (1) the date DEA receives HHS's scientific and medical evaluation/scheduling recommendation, or (2) the date DEA receives notice of the NDA approval by HHS. Subsection 811(j)(3) specifies that the rulemaking shall become immediately effective as an IFR without requiring DEA to demonstrate good cause therefore. Thus, the purpose of subsection 811(j) is to speed the process by which DEA schedules newly approved drugs that are

[3] 21 CFR 1308.44(b), 1316.53.

currently either in schedule I or not controlled (but which have sufficient abuse potential to warrant control) so that such drugs may be marketed without undue delay following FDA approval.[4]

Subsection 811(j)(3) further provides that the IFR shall give interested persons the opportunity to comment and to request a hearing. After the conclusion of such proceedings, DEA must issue a final rule in accordance with the scheduling criteria of 21 U.S.C. 811(b) through (d), and 812(b).

Zuranolone (chemically known as 1-[2-[(3*R*,5*R*,8*R*,9*R*,10*S*,13*S*,14*S*,17*S*)-3-hydroxy-3,13-dimethyl-2,4,5,6,7,8,9,10,11,12,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl]-2-oxoethyl]pyrazole-4-carbonitrile) is a new molecular entity with CNS activity. Zuranolone is a positive allosteric modulator of gamma-aminobutyric acid type A ($GABA_A$) receptors and an inhibitory neurosteroid substance that shares structural features and a pharmacological mechanism of action with progesterone, alfaxalone (schedule IV), and brexanolone (allopregnanolone, schedule IV).

On December 5, 2022, Sage Therapeutics, Inc. submitted an NDA for zuranolone to FDA. On August 4, 2023, FDA approved the NDA for zuranolone to be marketed as a prescription drug (ZURZUVAE, capsule) for the treatment of post-partum depression. DEA received notification that FDA approved the NDA on the same date. Pursuant to its FDA-approved prescription drug labeling, ZURZUVAE, 50 mg, is to be administered orally once in the evening with fat-consuming food for 14 days. The dose may be reduced for patients who cannot tolerate 50 mg.

Determination to Schedule Zuranolone

[4] Given the parameters of subsection 811(j), in DEA's view, it would not apply to a reformulation of a drug containing a substance currently in schedules II through V for which an NDA has recently been approved.

On July 12, 2023, DEA received from HHS a scientific and medical evaluation entitled "Basis for the Recommendation to Control Zuranolone and its Salts in Schedule IV of the Controlled Substances Act" and a scheduling recommendation. Pursuant to 21 U.S.C. 811(b) and (c), this document contained an eight-factor analysis of the abuse potential, legitimate medical use, and dependence liability of zuranolone, along with HHS's recommendation to control zuranolone and its salts under schedule IV of the CSA.

In response, DEA reviewed the scientific and medical evaluation and scheduling recommendation provided by HHS, along with all other relevant data, and completed its own eight-factor review pursuant to 21 U.S.C. 811(c). DEA concluded that zuranolone meets the 21 U.S.C. 812(b)(4) criteria for placement in schedule IV of the CSA.

Pursuant to subsection 811(j), and based on HHS's scheduling recommendation, the approval of the NDA by HHS/FDA, and DEA's determination, DEA is issuing this IFR to schedule zuranolone as a schedule IV controlled substance under the CSA.

Included below is a brief summary of each factor as analyzed by HHS and DEA, and as considered by DEA in its scheduling action. Please note that both DEA and HHS analyses are available in their entirety under "Supporting Documents" in the public docket for this IFR at *https://www.regulations.gov*, under Docket Number "DEA1258." Full analysis of, and citations to, the information referenced in the summary may also be found in the supporting and related material.

1. Its Actual or Relative Potential for Abuse

Zuranolone is a new molecular entity that has not been marketed in the United States or any country. Thus, evidence regarding its diversion, illicit manufacturing, or deliberate ingestion is currently lacking. DEA notes that there are no reports of law enforcement encounters of zuranolone in the National Forensic Laboratory Information

System (NFLIS)-Drug database.[5] Zuranolone has sedative effects and is likely to have abuse potential, similar to schedule IV sedatives such as alprazolam. Thus, it is reasonable to assume that zuranolone may be diverted from legitimate channels, used contrary to or without medical advice, and capable of creating hazards to the users and to the safety of the community. In human abuse potential studies, zuranolone produced positive subjective responses that are similar to those produced by alprazolam (schedule IV). Zuranolone produces rewarding effects that are comparable to those produced by schedule IV sedatives; therefore, zuranolone is likely to be abused for its sedative effects contrary to medical advice.

2. Scientific Evidence of Its Pharmacological Effects, if Known

Zuranolone is a selective neuroactive steroid that potentiates synaptic (γ subunit-containing) and extra synaptic (δ-subunit containing) $GABA_A$ receptor activity. Zuranolone acts on $GABA_A$ receptors to enhance the effects of GABA, a major inhibitory neurotransmitter in the CNS. Zuranolone acts directly through the $GABA_A$ receptor-channel complex to increase the probability that the channel will enter into naturally occurring open states of relatively long duration and allow the influx of chloride. Zuranolone was found to potentiate GABA-evoked current in cells expressing human $GABA_A$ receptor subtypes. HHS noted that these data are consistent with a mechanism of action of zuranolone that is similar to other schedule IV neurosteroids (e.g., brexanolone) as a positive allosteric modulator of $GABA_A$ sites.

In animal studies, zuranolone's effect on the general behavioral profile in male rats showed that it produced behavioral activities, such as decreased activity, ataxia, hypersensitivity to touch and/or sound, and impaired righting reflex at supratherapeutic

[5] NFLIS-Drug is a comprehensive information system that includes data from forensic laboratories that handle more than 96% of an estimated 1 million distinct annual State and local drug analysis cases. NFLIS-Drug includes drug chemistry results from completed analyses only. While NFLIS-Drug data is not direct evidence of abuse, it can lead to an inference that a drug has been diverted and abused. *See* 76 FR 77330, 77332 (Dec. 12, 2011). NFLIS data were queried on August 30, 2023.

plasma concentrations. The observations were generally limited to the highest dose test (22.5 mg/kg), although some animals exhibited slight impairments at the lower doses tested (3 and 10 mg/kg).

In a drug discrimination study using male rats trained to discriminate midazolam and saline, intraperitoneally administered zuranolone (0.1, 0.3, 0.5, 1, and 3 mg/kg) produced dose-dependent effects and full substitution to midazolam discriminative stimulus effect at the highest dose tested when considering lever presses over the entire session and not just the first reinforcer (75 percent). However, 3 mg/kg zuranolone produced behavioral impairment, such that only five of ten rodents completed the session. In female rats, intraperitoneally administered zuranolone (0.1, 0.3, 0.5, 1, and 2 mg/kg) also produced dose-dependent effects and full substitution to midazolam discriminative stimulus effect at the highest dose tested when considering lever presses over the entire session and not just the first reinforcer (72.5 percent).

Zuranolone reinforcing properties were assessed by determining whether self-administration behavior was maintained when the drug was substituted for cocaine (schedule II). As stated by HHS in their scientific and medical evaluation, the study found that the selected doses of zuranolone did not maintain robust self-administration in animals with a previous history of cocaine self-administration.

In clinical trials, zuranolone produced significantly greater mean drug liking than placebo. The low (30 mg) and middle (60 mg) doses of zuranolone produced significantly less mean drug liking scores than both alprazolam (schedule IV) doses (1.5 and 3 mg). However, the highest dose of zuranolone produced mean drug liking scores that were similar to both doses of alprazolam (schedule IV).

Zuranolone produced euphoria-related adverse events that are supportive of zuranolone having an abuse potential. However, the abuse-related treatment emergent

AE profile of zuranolone was slightly lower than that of alprazolam (a schedule IV benzodiazepine) at a supratherapeutic dose of zuranolone.

Zuranolone produced incidence of euphoria-related adverse events supportive of its abuse potential in animals and humans similar to those of benzodiazepines in schedule IV. These data are consistent with the fact that both drugs share a common mechanism of action involving positive allosteric modulation of the $GABA_A$ receptors.

3. The State of Current Scientific Knowledge Regarding the Drug or Other Substance

Zuranolone, chemically known as 1-[2-[(3*R*,5*R*,8*R*,9*R*,10*S*,13*S*,14*S*,17*S*)-3-hydroxy-3,13-dimethyl-2,4,5,6,7,8,9,10,11,12,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl]-2-oxoethyl]pyrazole-4-carbonitrile, is a new molecular entity.

Zuranolone is a drug product formulated as 20, 25, and 30 mg colored hard-gelatin capsules. The powder is white to off-white in color. Zuranolone is available as an immediate-release formulation and is absorbed with a time to maximum effect of approximately 6 hours and a half-life of 20 hours.

As discussed in the background section, zuranolone has an accepted medical use in the United States.

4. Its History and Current Pattern of Abuse

There is no information on the history and current pattern of abuse for zuranolone, since it has not been marketed, legally or illegally, in the United States or any other country. There is no evidence of diversion of zuranolone that has been distributed for research, such as for clinical trials. Data from preclinical and clinical studies indicate that the abuse potential of zuranolone is similar to that of schedule IV sedatives, including benzodiazepines. Consistent with the fact that zuranolone is a new molecular entity, the NFLIS-Drug database had no records of encounters by law enforcement.

In summary, pharmacological data on zuranolone show that it produces abuse-related effects and has an abuse potential similar to that of schedule IV CNS depressants.

5. The Scope, Duration, and Significance of Abuse

A search by DEA of the NFLIS-Drug database found no evidence of law enforcement encounters of zuranolone in the United States. Data from preclinical and clinical studies showed that zuranolone has an abuse potential that is similar to that of schedule IV sedatives, including benzodiazepines. Upon availability of zuranolone in the market, it is likely to be abused.

6. What, if any, Risk There Is to the Public Health

Zuranolone's abuse potential, similar to that of schedule IV sedatives, is an indication of its public health risk. As such, upon availability for marketing, it is likely to pose risk to public health comparable to schedule IV positive allosteric modulators of the $GABA_A$ receptor such as brexanolone and benzodiazepines. According to evaluation of public health risks conducted by HHS, the most observed adverse effects were somnolence, dizziness, and sedation. An overdose of zuranolone could result in sedation with or without respiratory depression or other severe adverse effects. Two simulated driving studies demonstrated impairment approximately 9 hours after nighttime administration.

Concomitant use with other CNS depressants such as alcohol may potentiate the impairment of psychomotor performance and cognition. HHS noted that zuranolone is not recommended for chronic administration; it is intended for a 14-day treatment course. This may lessen some public health risks compared to other drugs that are prescribed for longer durations or in larger quantities.

7. Its Psychic or Physiological Dependence Liability

Zuranolone's psychic and physiological dependence liability was assessed using data from animal physical dependence studies and clinical evaluations of physical dependence, including measures of withdrawal. As described by HHS, data from a

physiologic dependence study conducted in rats demonstrated zuranolone did not induce significant withdrawal-related phenotypes at the doses tested; however, zuranolone produced significant toxic effects in dogs, including convulsions and death in the dog toxicity studies. HHS noted the toxic effects in dogs, such as the early mortalities, may be consistent with withdrawal-type effects observed after cessation of chronic dosing of sedative-hypnotic benzodiazepines.

In clinical trials, when zuranolone was administered at therapeutic doses (≤ 50 mg/day) for a minimum of five days, it produced mild-to-moderate withdrawal-related effects in healthy individuals upon abrupt drug discontinuation, including the following: insomnia, palpitations, decreased appetite, nightmare, nausea, hyperhidrosis, and paranoia. Similar effects were not evident in the patient population. HHS provided caveats for why this may be the case, such as the withdrawal effects may have been obscured by the symptoms of the underlying condition (post-partum depression and major depressive disorder) or inadequate assessment of withdrawal in the various Phase 3 studies. However, based on available data provided by HHS, the withdrawal-related symptoms produced by zuranolone after abrupt drug discontinuation are similar to those that are clinically known for benzodiazepines in schedule IV.

The data taken together suggest that zuranolone maybe produce physical dependence, and the risk of physical dependence and withdrawal syndrome upon drug discontinuation is expected to be more severe for individuals who take a higher than the therapeutic dose of zuranolone for an extended period of time, which may include convulsions based on the dog toxicity studies.

8. Whether the Substance is an Immediate Precursor of a Substance Already Controlled under the CSA

Zuranolone is not an immediate precursor of any controlled substance, as defined by 21 U.S.C. 802(23).

Conclusion: After considering the scientific and medical evaluation and scheduling recommendation provided by HHS, and its own eight-factor analysis, DEA has determined that these facts and all relevant data constitute substantial evidence of potential for abuse of zuranolone. As such, DEA hereby schedules zuranolone as a controlled substance under the CSA.

Determination of Appropriate Schedule

The CSA lists the findings required to place a drug or other substance in any particular schedule (I, II, III, IV, or V).[6] After consideration of the analysis and recommendation of the Assistant Secretary for Health of HHS and review of all available data, the Administrator of DEA, pursuant to 21 U.S.C. 812(b)(4), finds that:

(1) Zuranolone has a potential for abuse similar to the drugs or other substances in schedule IV.

Zuranolone, a neuroactive steroid, is a positive allosteric modulator of $GABA_A$ receptors and produces sedation in general behavioral studies. In a drug discrimination study in animals, zuranolone produced dose-dependent substitution for midazolam (schedule IV) when considering the full session (partial substitution when considering the first reinforcer), demonstrating it has GABA agonist properties. Zuranolone produced positive subjective responses and euphoria-related adverse events similar to that of alprazolam (schedule IV), and greater than that of placebo in a human abuse potential study.

Furthermore, data from other clinical studies show that zuranolone produced incidence of euphoria-like adverse events in 5 percent of healthy individuals, including euphoric mood, feeling drunk, feeling of relaxation, feeling abnormal, and inappropriate effect compared to no incidence following placebo. Therefore, zuranolone has the potential for

[6] 21 U.S.C. 812(b).

abuse similar to alprazolam, midazolam, methohexital, and other substances in schedule IV.

(2) Zuranolone has a currently accepted medical use in treatment in the United States.

FDA approved the NDA for ZURZUVAE (zuranolone) as a treatment for post-partum depression. Thus, zuranolone has a currently accepted medical use in treatment in the United States.

(3) Abuse of zuranolone may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in schedule III but similar to other substances in schedule IV.

Zuranolone shares a similar pharmacology profile with brexanolone (schedule IV) and benzodiazepines (schedule IV). Data from a rat physical dependence study demonstrated that discontinuation of chronic administration of zuranolone at the doses tested did not produce physical dependence or withdrawal syndrome. In a dog toxicity study, drug discontinuation after chronic administration at supratherapeutic doses produced convulsions similar to that of benzodiazepines. Further, upon abrupt discontinuation in humans at the therapeutic dose (≤ 50 mg per day), zuranolone produced mild to moderate withdrawal-like effects in healthy individuals no worse than what is clinically known for schedule IV benzodiazepines. HHS concluded that there would be higher risk of developing physical dependence and withdrawal syndrome and more severe effects after abrupt drug discontinuation in individuals that took more than the therapeutic dose or for an extended duration. Withdrawal symptoms from physical dependence may include convulsions. Zuranolone produced positive subjective responses and euphoria-related adverse events and may produce psychic dependence. Zuranolone may lead to physical or psychological dependence similar to benzodiazepines in schedule IV.

Based on these findings, the Administrator concludes that zuranolone warrants control in schedule IV of the CSA.[7]

Requirements for Handling Zuranolone

Zuranolone is subject to the CSA's schedule IV regulatory controls and administrative, civil, and criminal sanctions applicable to the manufacture, distributing, dispensing, importing, exporting, research, and conduct of instructional activities, including the following:

1. *Registration.* Any person who handles (manufactures, distributes, reverse distributes, dispenses, imports, exports, engages in research, or conducts instructional activities or chemical analysis with, or possesses) zuranolone must be registered with DEA to conduct such activities pursuant to 21 U.S.C. 822, 823, 957, and 958, and in accordance with 21 CFR parts 1301 and 1312. These registration requirements, however, are not applicable to patients (end users) who possess zuranolone pursuant to a lawful prescription.

2. *Disposal of Stocks.* Any person unwilling or unable to obtain a schedule IV registration must surrender all quantities of currently held zuranolone, or may transfer all quantities of currently held zuranolone to a person registered with DEA. Zuranolone is required to be disposed of in accordance with 21 CFR part 1317, in addition to all other applicable Federal, state, local, and tribal laws.

3. *Security.* Zuranolone is subject to schedule III-V security requirements for DEA registrants and must be handled and stored in accordance with 21 CFR 1301.71-1301.77, pursuant to 21 U.S.C. 823, 821, 871(b). Non-practitioners handling zuranolone must also comply with the employee screening requirements of 21 CFR 1301.90-1301.93. These requirements, however, are not applicable to patients (end users) who possess zuranolone pursuant to a lawful prescription.

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[7] 21 U.S.C. 812(b)(4).

4. *Labeling and Packaging.* All labels and packaging for commercial containers of zuranolone must comply with 21 U.S.C. 825 and 958(e), and be in accordance with 21 CFR part 1302.

5. *Inventory.* Every DEA registrant who possesses any quantity of zuranolone must have an initial inventory of all stocks of controlled substances (including zuranolone) on hand on the date the registrant first engages in the handling of controlled substances, pursuant to 21 U.S.C. 827, and in accordance with 21 CFR 1304.03, 1304.04, and 1304.11.

Any person who registers with DEA to handle zuranolone must take an initial inventory of all stocks of controlled substances (including zuranolone) on hand on the date the registrant first engages in the handling of controlled substances, pursuant to 21 U.S.C. 827 and 958(e), and in accordance with 21 CFR 1304.03, 1304.04, and 1304.11(a) and (b).

After the initial inventory, every DEA registrant must take inventory of all controlled substances (including zuranolone) on hand every two years, pursuant to 21 U.S.C. 827, and in accordance with 21 CFR 1304.03, 1304.04, and 1304.11. These requirements, however, are not applicable to patients (end users) who possess zuranolone pursuant to a lawful prescription.

6. *Records and Reports.* DEA registrants must maintain records and submit reports for zuranolone, pursuant to 21 U.S.C. 827, 832(a), and 958(e), and in accordance with 21 CFR 1301.74(b) and (c) and parts 1304, 1312, and in accordance with 21 CFR 1301.74(b) and (c) and parts 1304, 1312, and 1317.

7. *Prescriptions.* All prescriptions for zuranolone, or products containing zuranolone, must comply with 21 U.S.C. 829, and be issued in accordance with 21 CFR parts 1306 and 1311, subpart C.

8. *Manufacturing and Distributing.* In addition to the general requirements of the CSA and DEA regulations that are applicable to manufacturers and distributors of schedule IV controlled substances, such registrants should be advised that (consistent with the foregoing considerations) any manufacturing or distribution of zuranolone may only be for the legitimate purposes consistent with the drug's labeling, or for research activities authorized by the Federal Food, Drug, and Cosmetic Act (FDCA), as applicable, and the CSA.

9. *Importation and Exportation.* All importation and exportation of zuranolone must be in compliance with 21 U.S.C. 952, 953, 957, and 958, and in accordance with 21 CFR part 1312.

10. *Liability.* Any activity involving zuranolone not authorized by, or in violation of, the CSA or its implementing regulations, is unlawful, and may subject the person to administrative, civil, and/or criminal sanctions.

Regulatory Analyses

Administrative Procedure Act

Section 553 of the APA (5 U.S.C. 553) generally requires notice and comment for rulemakings. However, 21 U.S.C. 811(j) provides that in cases where a certain new drug is (1) approved by HHS, under section 505(c) of the FDCA, and (2) HHS recommends control in CSA schedule II-V, DEA shall issue an IFR scheduling the drug within 90 days. As stated in the legal authority section, the 90-day time frame is the later of: (1) the date DEA receives HHS's scientific and medical evaluation/scheduling recommendation, or (2) the date DEA receives notice of the NDA approval by HHS. Additionally, subsection 811(j) specifies that the rulemaking shall become immediately effective as an IFR without requiring DEA to demonstrate good cause.

Executive Orders 12866, 13563, and 14094, Regulatory Review

In accordance with 21 U.S.C. 811(a), this scheduling action is subject to formal

rulemaking procedures performed "on the record after opportunity for a hearing," which are conducted pursuant to the provisions of 5 U.S.C. 556 and 557. The CSA sets forth the procedures and criteria for scheduling a drug or other substance. Such actions are exempt from review by the Office of Management and Budget pursuant to section 3(d)(1) of Executive Order (E.O.) 12866 and the principles reaffirmed in E.O. 13563. E.O. 14094 modernizes the regulatory review process to advance policies that promote the public interest and address national priorities.

Executive Order 12988, Civil Justice Reform

This meets the applicable standards set forth in sections 3(a) and 3(b)(2) of E.O. 12988 to eliminate drafting errors and ambiguity, minimize litigation, provide a clear legal standard for affected conduct, and promote simplification and burden reduction.

Executive Order 13132, Federalism

This rulemaking does not have federalism implications warranting the application of E.O. 13132. The proposed rule does not have substantial direct effects on the states, on the relationship between the National Government and the states, or on the distribution of power and responsibilities among the various levels of government.

Executive Order 13175, Consultation and Coordination with Indian Tribal Governments

This rule does not have tribal implications warranting the application of E.O. 13175. It does not have substantial direct effects on one or more Indian tribes, on the relationship between the Federal Government and Indian tribes, or on the distribution of power and responsibilities between the Federal Government and Indian tribes.

Paperwork Reduction Act

This proposed action does not impose a new collection of information requirement under the Paperwork Reduction Act, 44 U.S.C. 3501–3521.

Regulatory Flexibility Act

The Regulatory Flexibility Act (RFA) (5 U.S.C. 601-612) applies to rules that are subject to notice and comment under section 553(b) of the APA. As noted in the above discussion regarding the applicability of the APA, DEA is not required to publish a general notice of proposed rulemaking. Consequently, the RFA does not apply to this IFR.

Unfunded Mandates Reform Act of 1995

In accordance with the Unfunded Mandates Reform Act (UMRA) of 1995, 2 U.S.C. 1501 *et seq.,* DEA has determined and certifies that this proposed action would not result in any Federal mandate that may result "in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any 1 year * * *." Therefore, neither a Small Government Agency Plan nor any other action is required under UMRA of 1995.

Congressional Review Act

This rule is not a major rule as defined by the Congressional Review Act (CRA), 5 U.S.C. 804. However, pursuant to the CRA, DEA is submitting a copy of this IFR to both Houses of Congress and to the Comptroller General.

Signing Authority

This document of the Drug Enforcement Administration was signed on October 25, 2023, by Administrator Anne Milgram. That document with the original signature and date is maintained by DEA. For administrative purposes only, and in compliance with requirements of the Office of the Federal Register, the undersigned DEA Federal Register Liaison Officer has been authorized to sign and submit the document in electronic format for publication, as an official document of DEA. This administrative process in no way alters the legal effect of this document upon publication in the Federal Register.

Scott Brinks,
Federal Register Liaison Officer,
Drug Enforcement Administration.

List of Subjects in 21 CFR Part 1308

Administrative practice and procedure, Drug traffic control, Reporting and recordkeeping requirements.

For the reasons set out above, DEA amends 21 CFR part 1308 as follows:

PART 1308—SCHEDULES OF CONTROLLED SUBSTANCES

1. The authority citation for 21 CFR part 1308 continues to read as follows:

Authority: 21 U.S.C. 811, 812, 871(b), 956(b) unless otherwise noted.

2. In § 1308.14:

a. Add a new paragraph (c)(60) to read as follows:

§ 1308.14 Schedule IV.

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